REVIEW ARTICLE

LESS IS MORE

Initial Coronary Stent Implantation With Medical Therapy vs Medical Therapy Alone for Stable Coronary Artery Disease

Meta-analysis of Randomized Controlled Trials

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Background: Prior meta-analyses have yielded conflicting results regarding the outcomes of treatment of stable coronary artery disease (CAD) with initial percutaneous coronary intervention (PCI) vs medical therapy. However, most of the studies in prior systematic reviews used balloon angioplasty as well as medical therapies that do not reflect current interventional or medical practices. We therefore performed a meta-analysis of all randomized clinical trials comparing initial coronary stent implantation with medical therapy to determine the effect on death, nonfatal myocardial infarction (MI), unplanned revascularization, and persistent angina.

Methods: Prospective randomized trials were identified by searches of the MEDLINE database from 1970 to September 2011. Trials in which stents were used in less than 50% of PCI procedures were excluded. Data were extracted from each study, and summary odds ratios (ORs) were obtained using a random effects model.

Results: Eight trials enrolling 7229 patients were identified. Three trials enrolled stable patients after MI, whereas 5 studies enrolled patients with stable angina and/or ischemia on stress testing. Mean weighted follow-up was 4.3 years. The respective event rates for death with stent implantation and medical therapy were 8.9% and 9.1% (OR, 0.98; 95% CI, 0.84-1.16); for nonfatal MI, 8.9% and 8.1% (OR, 1.12; 95% CI, 0.93-1.34); for unplanned revascularization, 21.4% and 30.7% (OR, 0.78; 95% CI, 0.57-1.06); and for persistent angina, 29% and 33% (OR, 0.80; 95% CI, 0.60-1.05).

Conclusion: Initial stent implantation for stable CAD shows no evidence of benefit compared with initial medical therapy for prevention of death, nonfatal MI, unplanned revascularization, or angina.

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PERCUTANEOUS CORONARY INtervention (PCI) reduces death and nonfatal myocardial infarction (MI) in the setting of acute coronary syndromes.[1,2] However, the role of PCI in treatment of stable coronary artery disease (CAD) remains controversial.[3,4] Despite recent studies clearly demonstrating that initial PCI offers no benefit in terms of reducing death or other cardiovascular events over optimal medical therapy in the setting of nonacute CAD,[5-7] these findings have not been incorporated into clinical practice.[8,9] Perhaps contributing to the ambiguity, recent meta-analyses have yielded conflicting results regarding the impact of PCI on survival of patients with stable CAD.[10,11] These meta-analyses included studies that enrolled patients in the 1980s and 1990s, an era when balloon angioplasty was the predominant form of PCI. Since that time, interventional practice has evolved toward the placement of coronary stents whenever technically feasible to prevent acute vessel closure and restenosis. Medical therapy has advanced over the last 20 years as well. For example, medical treatment in the Angioplasty Compared with Medicine (ACME) trial,[12] which enrolled patients from 1987 to 1990 included aspirin, nitrates, β-blockers, and calcium channel blockers[12] but did not include 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins), angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers, which are now considered essential components of optimal medical therapy.[13] We therefore performed a systematic review and meta-analysis of randomized clinical trials that compared initial stent implantation and medical therapy with a strategy of initial medical therapy alone to determine the ef-

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Table 1. Outcome Definitions

Study	Death	Nonfatal MI	Unplanned Revascularization	Persistent Angina
TOAT[16]	ND	ND	ND	NR; elective revascularization
Hambrecht et al[17]	Cardiac death	ND	CABG, PTCA of target lesion or other coronary segments	NR; hospitalization and coronary angiography for worsening angina
DECOPI[18]	Total mortality	ECG, symptoms and cardiac enzyme abnormality	ND	CCS class >1 angina
OAT[5,19]	Death from any cause	2 or 3 of symptoms: >30 min, ECG changes, elevated cardiac biomarkers (CK ≥2 × ULN, CK-MB >ULN, troponin I or T >2 × ULN); for reinfarction after revascularization: elevated cardiac marker defined as >3 × ULN for PCI patients and >5 × ULN for CABG patients	PCI or CABG excluding protocol-assigned PCI	Angina on Rose angina questionnaire
MASS II[14]	Overall mortality	Q-wave MI	Additional PCI or CABG after index procedure	Angina symptoms at 5-y follow-up
COURAGE[6,20]	Death from any cause	Spontaneous: consistent clinical presentation, new abnormal Q-waves, CK-MB ≥1.5 × ULN; troponin I or T ≥2 × ULN; silent MI defined by abnormal Q-waves; Post-PCI: CK-MB ≥3 × ULN; troponin I or T ≥5 × ULN associated with new ischemic symptoms; post-CABG: CK-MB, troponin I or T ≥10 × ULN	Additional PCI or CABG or PCI	Seattle Angina Questionnaire
JSAP[21]	Death from any cause	New abnormal Q-waves or clinical history with ECG changes, cardiac enzymes >2 × ULN	Elective or emergency vascularization	Modified CCS classification
BARI 2D[7,22]	Death from any cause	Spontaneous: 2-fold increase in CK-MB or troponin, ischemia by symptoms, ECG or imaging; post-PCI: CK-MB >3 × ULN; silent: Q-wave change >2 grades	First PCI or CABG done during follow-up	Angina in patients with angina at entry

Abbreviations: BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CABG, coronary artery bypass graft surgery; CCS, Canadian Cardiovascular Society[23]; CK, creatine kinase; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; DECOPI, Desobstruction Coronaire en Post-Infarctus; ECG, electrocardiogram; JSAP, Japanese Stable Angina Pectoris Study; MASS, Medicine, Angioplasty, or Surgery Study; MB, MB fraction of CK; MI, myocardial infarction; ND, not described; NR, not reported; OAT, Occluded Artery Trial; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; TOAT, The Open Artery Trial; ULN, upper limit of normal.

fect of contemporary interventional and medical therapy on outcomes of patients with stable CAD.

METHODS

SEARCH STRATEGY

A systematic search of published studies in any language in MEDLINE from 1970 to September 2011 was performed independently by both authors. Search terms included *stent, medical therapy, stable angina, coronary artery disease*, as well as combinations. A filter for randomized controlled trials was used. In addition, bibliographies of retrieved articles and prior reviews on the subject were searched for other relevant studies.

INCLUSION CRITERIA

For inclusion, studies were required to be prospective, randomized trials of PCI plus medical therapy vs medical therapy alone in patients with stable CAD with the individual outcomes of death and nonfatal MI reported at a minimum follow-up of 1 year. Stent implantation had to exceed 50% of PCI procedures for inclusion. Although studies randomizing patients with acute coronary syndromes were excluded from the analysis, studies of stable patients following a completed MI were included. Studies were included regardless of the presence of documented ischemia or any functional assessment of the hemodynamic significance of a coronary stenosis. For studies in which medical therapy was compared against separate arms of PCI or coronary artery bypass graft (CABG) surgery,[7,14] only the comparison of medical therapy vs stent implantation was extracted.

DATA EXTRACTION

Patient characteristics, study design, and outcomes were systematically reviewed and recorded independently by each author. Discrepancies were resolved by consensus. Study quality was evaluated according to the criteria of Jadad et al.[15]

OUTCOMES

The following clinical outcomes were analyzed: death from any cause (unless only cardiac death was reported); nonfatal MI (or reinfarction in the studies that enrolled post-MI patients); unplanned revascularization (PCI or CABG) during follow-up; and persistent angina. For each outcome, we used data available from the longest follow-up available to a maximum of 5 years. End point definitions were those used in the individual trials and are summarized in **Table 1**. Postprocedural MI, when identified, was included as a nonfatal MI event. Unplanned revascularization included any PCI or CABG excluding the PCI mandated by initial randomization. Persistent angina was an-

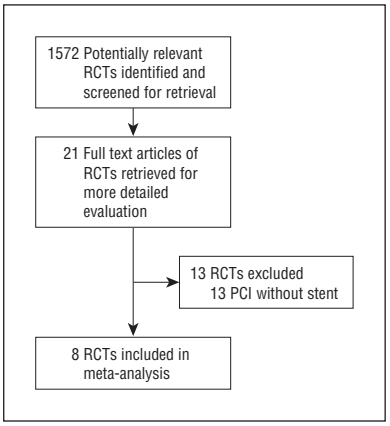

Figure 1. Flow diagram of selection of studies included in the meta-analysis.

Table 2. Randomized Trials of Stent Implantation vs Medical Therapy in Patients With Stable Coronary Artery Disease

Source	Patients, No.	Enrollment Years	Follow-up, y	Enrollment Criteria
TOAT,[16] 2002	66	1997-1999	1	Q-wave anterior MI with persistent occlusion of the LAD and absence of chest pain
Hambrecht et al,[17] 2004	101	1997-2001	1	Stable angina with documented ischemia
DECOPI,[18] 2004	212	1998-2001	3	Stable patients within 15 d of Q-wave MI, no ischemia, and total occlusion of the infarct-related artery
OAT,[5] 2006	2166	2000-2005	4	Stable patients 3 to 28 d after MI with total occlusion of the infarct-related artery
MASS II,[14] 2007	408	1995-2000	5	Stable angina or ischemia on stress test
COURAGE,[6] 2007	2287	1999-2004	4.6	Stable angina; stabilized unstable angina; myocardial ischemia or stenosis >80%
JSAP,[21] 2008	384	2002-2004	3.3	Stable exertional angina or inducible ischemia; stenosis ≥75%
BARI 2D,[7] 2009	1605	2001-2005	5	Diabetes with inducible ischemia or angina

Abbreviations: BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; DECOPI, Desobstruction Coronaire en Post-Infarctus; JSAP, Japanese Stable Angina Pectoris Study; LAD, left anterior descending coronary artery; MASS, Medicine, Angioplasty, or Surgery Study; MI, myocardial infarction; OAT, Occluded Artery Trial; TOAT, The Open Artery Trial.

gina following randomization. The definition of angina was that used in the individual trials. In 3 studies,[5-7] this outcome was reported in ancillary publications.[19,20,22] When these definitions of angina were not specified, alternative end points consistent with angina were used, including hospitalization and coronary angiography for worsening angina in 1 study[16] and elective revascularization in 2 studies.[17,21]

STATISTICAL ANALYSIS

As patient-level data from each trial were not available, a meta-analysis of summary statistics from individual trials was performed using Comprehensive Meta Analysis software, version 2 (Biostat). Data were analyzed according to the intention-to-treat principle. The Cochrane Q statistic failed to indicate statistical heterogeneity for the outcomes of death and nonfatal MI, whereas statistical heterogeneity was present for the end points of unplanned revascularization and persistent angina. Since the absence of statistical heterogeneity does not indicate homogeneity, summary odds ratios (ORs) for all end points were calculated with the inverse variance method using a random effects model from the OR and 95% confidence interval (CI) for each end point in each study. The random effects model provides a more conservative summary estimate because it incorporates both within-trial and between-trial variance. $P<.05$ was considered statistically significant, and all tests were 2-sided.

A subgroup analysis of the 3 trials randomizing asymptomatic patients following MI was performed for each outcome. Sensitivity analyses were performed for each outcome to determine whether any single study disproportionally influenced the pooled estimate by excluding individual trials 1 at a time and recalculating the combined OR for the remaining studies. An additional sensitivity analysis was performed by including the 1 trial[17] with no mortality events in either group in the calculation of ORs by adding 0.5 to each cell.

To qualitatively assess publication bias, a funnel plot of the logarithm of effect size vs the standard error for each trial was generated. The Egger weighted linear regression test was used to examine the quantitative association between mean effect estimate and its variance.

RESULTS

LITERATURE SEARCH

The electronic search yielded 1572 citations, which were screened by reviewing the title or abstract of each. Of these, 21 publications were reviewed in full, and 8 trials were included in the meta-analysis (**Figure 1**). These were the Open Artery Trial (TOAT),[16] the Medicine, Angioplasty, or Surgery Study II (MASS II),[14] the trial by Hambricht et al,[17] Desobstruction Coronaire en Post-Infarctus (DECOPI),[18] the Occluded Artery Trial (OAT),[5] the Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation (COURAGE),[6] the Japan Stable Angina Pectoris (JSAP) Study[21] and Bypass Angioplasty Revascularization 2 Diabetes (BARI 2D)[7] (**Table 2**). The 8 trials enrolled 7229 patients between 1997 and 2005, of whom 3617 were randomized to stent treatment and medical therapy and 3612 were randomized to medical therapy alone. Three studies[5,16,18] exclusively enrolled stable patients with a recent MI to compare stenting of the infarct-related artery and medical therapy vs medical therapy alone. Baseline characteristics of the study populations are provided in **Table 3**.

Patients were predominately men. Diabetics made up 14% to 100% of the study populations. Mean ejection fractions ranged from 36% to 67%. Stents were implanted in 72% to 100% of patients. Drug-eluting stents were used in a minority of patients (2.7%-35%) in 3 studies.[5-7] Medical therapy including aspirin, β-blockers, ACE inhibitors, and statins were used in an increasing percentage of patients over time in all studies except JSAP,[21] which had very low utilization of β-blockers, ACE inhibitors and statins[21] (**Table 4**). The weighted mean duration of follow-up was 4.3 years.

Table 3. Patient Characteristics

Study	Age, Mean, y	Men, %	Diabetes, %	Previous MI, %	Ejection Fraction, %	Vessels Treated, No.	Stent Implanted, %	Drug-Eluting Stent, %
TOAT[16]	58	80	14	100	36	1	100	0
Hambrecht et al[17]	61	100	23	46	63	1	100	0
DECOPI[18]	57	85	15	100	50	1	80	0
OAT[5]	59	78	21	100	47	1	87	8
MASS II[14]	60	68	29	46	67	2.1	72	0
COURAGE[6]	61	85	33	38	61	1.6	94	2.7
JSAP[21]	64	75	40	15	65	1.1	99	0
BARI 2D[7]	62	68	100	30	57	1.5	91	35

Abbreviations: BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; DECOPI, Desobstruction Coronaire en Post-Infarctus; JSAP, Japanese Stable Angina Pectoris Study; MASS, Medicine, Angioplasty, or Surgery Study; MI, myocardial infarction; OAT, Occluded Artery Trial; TOAT, The Open Artery Trial.

Table 4. Medical Therapy in Included Studies[a]

	Aspirin		β-Blocker		ACE Inhibitor		Statin	
Study	Stent	Medical Therapy	Stent	Medical Therapy	Stent	Medical Therapy	Stent	Medical Therapy
TOAT[16]	100	100	84	82	100	100	100[b]	100[b]
Hambrecht et al[17]	98	98	86	88	88	74	80	72
DECOPI[18]	83	83	81	81	58	58	82	82
OAT[5]	97	94	86	89	80	80	80	82
MASS II[14]	80	80	61	68	30	29	73	68
COURAGE[6]	96	95	85	89	58	60	86	89
JSAP[21]	92	91	44	52	22	14	49	45
BARI 2D[7]	94	94	84	88	91	92	95	95

Abbreviations: ACE, angiotensin-converting enzyme; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; DECOPI, Desobstruction Coronaire en Post-Infarctus; JSAP, Japanese Stable Angina Pectoris Study; MASS, Medicine, Angioplasty, or Surgery Study; OAT, Occluded Artery Trial; TOAT, The Open Artery Trial.
[a] All data reported as percentages of patients.
[b] Lipid-lowering agents (specific drug class not mentioned).

Study quality is summarized in **Table 5**. None of the trials was blinded. All of the studies were randomized, and all but 1 study[21] reported on study withdrawals and described the completeness of follow-up.

QUANTITATIVE OUTCOMES

Of the total 649 deaths among the 7229 randomized patients, 322 occurred in the 3617 patients in the stent arms (8.9%), whereas 327 occurred in the 3612 patients in the medical therapy arms (9.1%). The OR for initial stent implantation vs medical therapy for mortality was 0.98 (95% CI, 0.84-1.16) (*P*=.83) (**Figure 2**A). Results were very similar when the study by Hambricht et al,[17] which had no mortality events in either the stent or medical therapy group, was included in the analysis (Figure 2B). Nonfatal MI was reported in 323 of 3617 patients in the stent arms (8.9%) compared with 291 of 3612 patients in the medical therapy arms (8.1%). The OR for nonfatal MI for stent implantation compared with initial medical therapy was 1.12 (95% CI, 0.93-1.34) (*P*=.22) (Figure 2C). Unplanned revascularization was performed in 774 of 3617 stent patients (21.4%) and in 1049 of 3420 medical therapy patients (30.7%). The OR for unplanned revascularization in the stent vs medical therapy patients was 0.78 (95% CI, 0.57-1.06) (*P*=.11) (Figure 2D). Data on angina status was available for 4122 patients. Among the patients randomized to initial stent implantation, 597 of 2070 experienced persistent angina (29%) compared with 669 of 2052 randomized to medical therapy (33%) (OR, 0.80; 95% CI, 0.60-1.05) (*P*=.10) (Figure 2E).

SUBGROUP ANALYSIS

There were no significant differences in the point estimates for death, unplanned revascularization, and freedom from angina between the studies of stable post-MI patients and the studies that randomized patients with angina or ischemia. However, the OR for nonfatal MI for stent placement compared with medical therapy was 1.49 (95% CI, 1.00-2.21) (*P*=.05) in the post-MI studies compared with 1.04 (95% CI, 0.84-1.28) (*P*=.73) in the stable angina/ischemia trials.

PUBLICATION BIAS AND SENSITIVITY ANALYSES

The funnel plot was symmetric, indicating a lack of publication bias (**Figure 3**). The Eggers test further supported the absence of publication bias with a 1-tailed *P* value of .45. Sensitivity analyses to assess

Table 5. Quality Metrics of Included Studies

Study	Study Blinding	Blinding Technique	Random Assignment	Withdrawal Descriptions
TOAT[16]	No	No	Yes	Yes
Hambrecht et al[17]	No	No	Yes	Yes
DECOPI[18]	No	No	Yes	Yes
OAT[5]	No	No	Yes	Yes
MASS II[14]	No	No	Yes	Yes
COURAGE[6]	No	No	Yes	Yes
JSAP[21]	No	No	Yes	No
BARI 2D[7]	No	No	Yes	Yes

Abbreviations: BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; DECOPI, Desobstruction Coronaire en Post-Infarctus; JSAP, Japanese Stable Angina Pectoris Study; MASS, Medicine, Angioplasty, or Surgery Study; OAT, Occluded Artery Trial; TOAT, The Open Artery Trial.

the potential impact of qualitative differences in study design and patient selection showed that exclusion of any single trial from the analysis for mortality, nonfatal MI, and freedom from angina did not alter the overall findings of the analysis. However, exclusion of TOAT,[16] Hambrecht et al,[17] or MASS II[14] from the analysis of unplanned revascularization changed the point estimate of the OR to favor initial stent implantation.

COMMENT

The significant finding of this analysis is that compared with a strategy of initial medical therapy alone, coronary stent implantation in combination with medical therapy for stable CAD is not associated with a significant reduction in mortality, nonfatal MI, unplanned revascularization, or angina after a mean follow-up of 4.3 years. These results are in contrast to 2 recent meta-analyses that found reductions in mortality[11] and angina[24] in patients assigned to initial PCI. However, a unique aspect of the current study is likely responsible for the divergent results. By limiting the analysis to studies in which stent implantation was the predominant form of PCI, this meta-analysis, for the first time that we know of, compares contemporary versions of PCI and medical therapy. The exclusion of studies using balloon angioplasty as the primary form of PCI shifted the years of enrollment forward by almost a decade during which time optimal medical therapy evolved to the current regimen that includes aspirin, β-blockers, ACE-inhibitors (or angiotensin receptor blockers), and statins.

The failure of stent implantation to reduce the risk of death or MI compared with medical therapy reinforces current concepts of the underlying pathophysiologic characteristics of atherosclerosis as a diffuse arterial inflammatory disease that gives rise to vulnerable plaques, the disruption of which leads to coronary thrombosis, MI, and death.[25] Lesions most prone to rupture tend to be those of the least hemodynamic consequence, whereas the obstructive lesions that are stented to treat angina or ischemia are paradoxically less prone to rupture.[25] The current findings fail to support theories suggesting that PCI reduces mortality by improving myocardial blood flow or stabilizing vulnerable plaque in patients with angina or by improving left ventricular remodeling or electrophysiologic stability in patients with an occluded artery following MI.[11,26] The loss of the earlier mortality benefit associated with an initial PCI strategy[11] is likely due to the widespread incorporation of potent antiplatelet and anti-atherosclerotic therapies into medical regimens, which has led to a substantial reduction in cardiovascular mortality over the past 20 years.[27]

The trend toward an increased risk of nonfatal MI in the stent group in the current analysis may reflect the fact that, depending on the diagnostic criteria used, PCI causes periprocedural MI in 5% to 30% of cases due to distal plaque embolization, side branch occlusion, and other mechanisms.[28] However, sensitive troponin assays were used to detect myocardial injury in only 2 of the 8 studies[6,7] included in this meta-analysis, which may explain why the risk of nonfatal MI was not significantly increased in the stent group. It is unclear why the risk of nonfatal MI was increased in the studies involving post-MI patients with arteries occluded by thrombus. It may be that PCI in these patients is more likely to cause distal embolization of thrombus resulting in infarction of downstream viable territories or occlusion of recruitable collaterals predisposing to reinfarction in the event of stent thrombosis.[5]

Unplanned revascularization by PCI or CABG in patients randomized to initial medical therapy occurs in 3 circumstances: for angina symptoms refractory to medical therapy (crossover), for symptomatic restenosis or graft failure at the site of the crossover PCI or CABG, or for the development of symptomatic hemodynamically significant de novo atherosclerotic lesions. In patients randomized to initial stent therapy, unplanned revascularization is generally required for symptomatic restenosis of the stent site or development of new hemodynamically significant lesions associated with ischemia. Since both groups received the same medical therapy, the development of de novo lesions should occur at the same rate in each group. That unplanned revascularization was not significantly different in initially stented patients compared with those randomized to initial medical therapy suggests that the number of crossover PCIs in the medical group approximates the number of restenosis events in the stent group.

Since elimination of any of 3 studies in which the stent group underwent more unplanned revascularizations than the medical therapy arm[14,16,17] resulted in a significant reduction in the OR for unplanned revascularization in the stent group, it would be expected that if drug-eluting stents had been widely used, results would have shifted toward a statistically significant reduction in

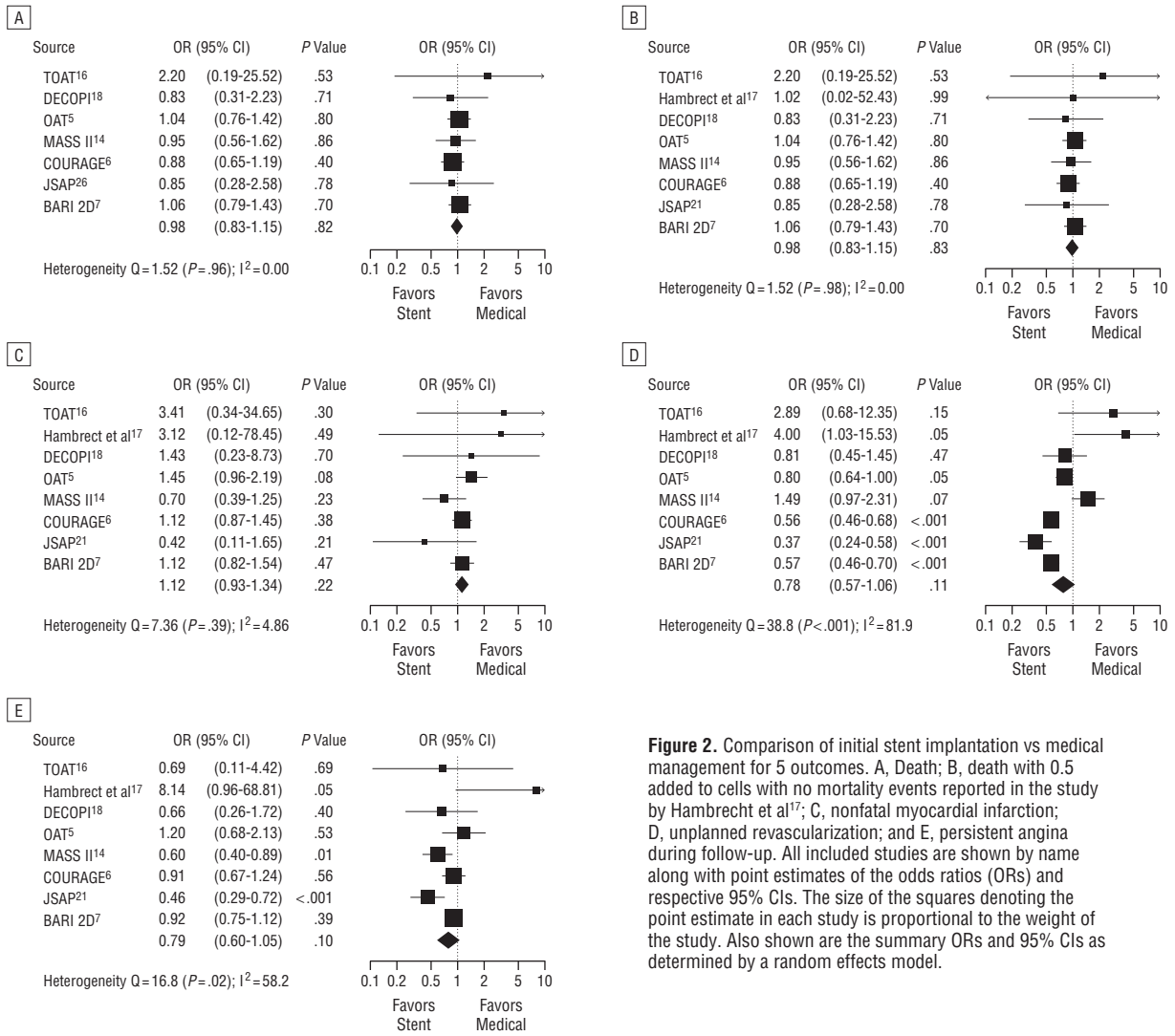

Figure 2. Comparison of initial stent implantation vs medical management for 5 outcomes. A, Death; B, death with 0.5 added to cells with no mortality events reported in the study by Hambrecht et al[17]; C, nonfatal myocardial infarction; D, unplanned revascularization; and E, persistent angina during follow-up. All included studies are shown by name along with point estimates of the odds ratios (ORs) and respective 95% CIs. The size of the squares denoting the point estimate in each study is proportional to the weight of the study. Also shown are the summary ORs and 95% CIs as determined by a random effects model.

unplanned revascularization with initial stent therapy.[29] However, from the perspective of resource utilization, 4391 total revascularization procedures were performed in the initial stent implantation group compared with 1049 revascularization procedures in patients randomized to initial medical therapy. Thus, any potential benefit accruing from a reduction of restenosis and subsequent unplanned revascularization that might be seen with initial drug-eluting stent treatment would still be greatly offset by the marked reduction in overall procedures in the medical therapy group. Furthermore, the use of drug-eluting stents might come at a cost of increases in death and MI from late stent thrombosis.[30]

Persistent angina is frequently the symptom that drives crossing over from medical therapy to PCI as well as the symptom that prompts evaluation for and detection of restenosis following PCI. Thus, the ability to render patients free of angina is a major factor that determines the need for revascularization in both the stent and medical therapy groups. It is noteworthy that this meta-analysis found no significant difference between stent and medical therapy arms with regard to this outcome. Early randomized trials of balloon angioplasty vs medical therapy[31-33] and a recent meta-analysis[24] that included these trials demonstrated greater reduction of angina with angioplasty than with medical therapy. The absence of a benefit in angina relief with stent implantation most likely indicates that the improvement in medical therapy for the treatment of angina superseded the improvement in angina reduction associated with the transition from balloon angioplasty to stent implantation. Furthermore, the antianginal drug ranolazine was not used in any of the studies included in this meta-analysis. Its use in combination with other antianginal agents would be expected to increase the numbers of patients free of angina[34] and thereby reduce the number of unplanned revascularizations in both stent and medical therapy arms.

Over 400 000 PCI procedures are performed for the treatment of stable CAD in the United States each year.[35] Despite publication of clinical trials and guidelines supporting the initial use of optimal medical therapy prior to PCI, only 44% of patients are treated with optimal medical therapy prior to PCI,[8] and approxi-

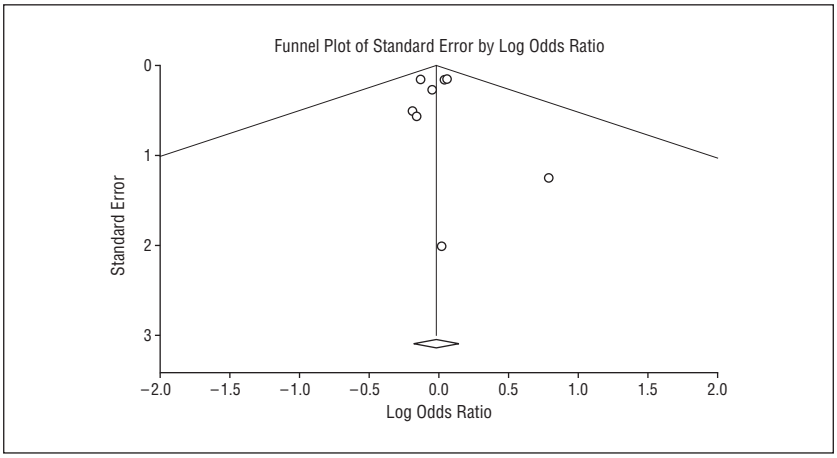

Figure 3. Assessment of publication bias. This funnel plot is a plot of a measure of study size on the vertical axis as a function of effect size on the horizontal axis for mortality. Large studies appear toward the top of the graph and tend to cluster near the mean effect size. Smaller studies appear toward the bottom of the graph and (since there is more sampling variation in effect size estimates in the smaller studies) will be dispersed across a range of values. In the absence of publication bias demonstrated here, the studies are distributed symmetrically about the combined effect size.

mately 50% of patients with an occluded infarct-related artery after an MI undergo PCI of that artery.[9] This resistance to adherence to recommendations derived from high quality evidence is multifactorial, including the fact that the existing data do not demonstrate the clear superiority of medical therapy for any clinical outcome. It has been suggested that financial rewards for physicians and hospitals to perform PCI in the fee-for-service health care environment of the United States may contribute to the persistent use of PCI in settings where it has been shown to offer no clinical benefit. In support of this concept, rates of PCI for stable CAD in Ontario, Canada, where a single-payer government-regulated system controls the annual volume of cardiac procedures, are less than half what they are in New York state.[36]

In the context of controlling rising health care costs in the United States, this study suggests that up to 76% of patients with stable CAD can avoid PCI altogether if treated with optimal medical therapy, resulting in a lifetime savings of approximately $9450 per patient in health care costs.[37] Furthermore, these findings imply that upstream testing to demonstrate ischemia in patients with stable angina symptoms may not be necessary.[38]

This study has several limitations. First, this is a meta-analysis of the pooled results reported from each individual trial because individual patient-level data were not available. Second, data were extracted only from randomized clinical trials. Patients enrolled in such trials may not be representative of patients actually seen in clinical practice. Third, although variables such as age and sex may be related to outcomes, these subgroup analyses could not be performed because outcomes stratified by age and sex were not included in the randomized trials included in this meta-analysis. Finally, as indicated by the confidence intervals, the absence of a detected difference between therapeutic strategies does not exclude the possibility of an undetected benefit or harm. However, given the absence of any detected benefit of stent placement on mortality and nonfatal MI, if subsets of patients such as those with more extensive areas of ischemia are identified who benefit from stent therapy,[39] there is likely to be another subset harmed to a similar degree by stent treatment.

In conclusion, the findings of this analysis support current recommendations for instituting optimal medical therapy in patients with stable CAD rather than proceeding directly to stent implantation.

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INVITED COMMENTARY

Mounting Evidence for Lack of PCI Benefit in Stable Ischemic Heart Disease

What More Will It Take to Turn the Tide of Treatment?

When treating patients with symptomatic coronary artery disease (CAD), clinicians frequently consider whether the initial management approach should be optimal medical therapy (OMT) alone or OMT in addition to coronary revascularization—generally percutaneous coronary intervention (PCI) in the vast majority of patients for whom revascularization would be considered. Over the past several years, several trials such as the Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation (COURAGE) Trial,[1] Bypass Angioplasty Revascularization 2 Diabetes Trial (BARI-2D),[2] and Japan Stable Angina Pectoris (JSAP) study[3] have challenged the conventional

wisdom that the triad of angina, objective evidence of myocardial ischemia, and the presence of 1 or more flow-limiting coronary stenoses necessitating revascularization are the *sine qua non* of optimal CAD management. In the aggregate, these studies have failed to show any incremental clinical benefit for PCI above and beyond OMT for the reduction of death or nonfatal myocardial infarction (MI), findings quite in contrast to those achieved with PCI in acute MI or high-risk patients with acute coronary syndrome (ACS).

In addition, there have been many meta-analyses of PCI vs OMT in patients with nonacute CAD that have purported to show evidence of a mortality reduction for myocardial revascularization compared with OMT, despite initial criticisms in the aftermath of the COURAGE Trial[1] that it told us nothing new, that PCI was already well known to not reduce death or MI in patients with stable CAD.[4] Schömig and coworkers[5] in 2008 published a meta-analysis in which they demonstrated a 20% mortality reduction in patients with stable coronary artery disease for PCI compared with OMT, yet this meta-analysis was extremely flawed in that it included trials of patients with acute MI and post-MI patients, which largely contributed to the mortality reduction attributed to PCI. In 2009, Jeremias et al[6] published a meta-analysis of 28 studies of nonacute CAD published from 1977 to 2007 that included 17 studies of PCI, 6 studies of coronary artery bypass graft (CABG) surgery, and 5 studies in which either PCI or CABG were compared with OMT; the study found a benefit on mortality but not on nonfatal MI for revascularization.[6]

The inclusion of both acute and post-MI trials comingled with stable angina and stable ischemic heart disease (SIHD) trials and revascularization (either PCI or CABG) was likewise a significant methodologic flaw because the purported mortality benefit was largely a function of the salutary effect of revascularization in acute and status post-MI patients, which completely distorts the conclusion that such patients with nonacute CAD derive a mortality benefit of revascularization. These shortcomings of meta-analyses by Schömig et al[5] and Jeremias et al[6] were addressed in a subsequent "corrected" meta-analysis in which Wijeysundera and coworkers[7] demonstrated quite convincingly that when the acute and post-MI trials as well as the trials that compared CABG to OMT were excluded from the meta-analyses that evaluated PCI vs OMT in patients with unstable angina, there indeed was no evidence for any mortality benefit with PCI.

In this issue of the *Archives*, we have yet another meta-analysis[8] in which 8 prospective randomized controlled trials (RCTs) involving 7229 patients compared initial coronary stent implantation with OMT to determine the effect of treatment assignment on death, nonfatal MI, unplanned revascularization, and persistent angina as the outcomes of interest during a mean weighted follow-up of 4.3 years. The respective event rates in stent implantation and medical therapy for death were 8.9% and 9.1%, (odds ratio [OR], 0.98; 95% CI, 0.84-1.16); for nonfatal MI, 8.9% and 8.1%, (OR, 1.12; 95% CI, 0.93-1.34); for unplanned revascularization, 21.4% and 30.7% (OR, 0.78; 95% CI, 0.57-1.06); and for persistent angina, 29% and 33% (OR, 0.80; 95% CI, 0.60-1.05).[8] In other words, when PCI with stenting was compared with aggressive, multifaceted, contemporary secondary prevention and lifestyle intervention (the very definition of *OMT*), no incremental benefit for PCI was observed for hard outcomes or for persistent angina. This meta-analysis restricted the pooled studies to those in which stents were used in more than 50% of randomized patients and in which more contemporary COURAGE-like optimal medical therapy was used as the comparator. Thus, studies that included patients treated with percutaneous transluminal coronary angioplasty or more minimalistic medical therapy were omitted.

What is the practicing clinician to take away from the present study[8] in the context of other published meta-analyses?[5-7] First, the totality of evidence does not support any demonstrable clinical benefit for PCI in patients with stable CAD in terms of reducing death, nonfatal MI, hospitalization for ACS, need for unplanned revascularization, and a durable, sustained effect on angina relief. While a great deal of attention has been focused more recently on the need to develop and implement appropriate use criteria for PCI, especially in patients with SIHD and chronic angina, the inescapable fact is that it is increasingly harder to justify use of PCI solely for angina relief in such patients—especially as an initial approach to management, and if medical therapy has not been first instituted (or if efforts to optimize pharmacologic treatment in those treated initially medically are not undertaken).

Second, given the notable lack of benefit on improving hard clinical outcomes, the continued practice of a PCI-first strategy compared with an OMT-first strategy in patients with stable CAD may lead to the performance of many unnecessary PCI procedures. In fact, Diamond and Kaul[9] have postulated that if even one-third of elective PCI procedures in patients with SIHD (300 000 to 500 000 PCIs annually) could be averted or deferred as a consequence of OMT, the cost saving associated with this approach could net $6 billion to $8 billion annually that could be redirected to more productive preventive cardiology initiatives.

Third, despite the enormous commitment by the US government and funding agencies to support comparative effectiveness research as the best approach to defining the most effective and cost-effective approaches to patient management, this policy-level imperative has not translated into changes in clinical practice, and trials such as COURAGE,[1] BARI-2D,[2] and others studies are seemingly ignored.[10] While physicians outwardly worship at the altar of evidence-based medicine, in reality, we more often tend to practice selective evidence-based medicine by adopting and embracing those trials and studies with results that reinforce our existing clinical practice preferences or biases, while we ignore or disdain the results of studies with results that are unpopular, conflict with our existing clinical practice beliefs, or collide with the conventional wisdom. Certainly, one explanation for the current management of SIHD is the existing fee-for-service model of physician and hospital reimbursement, which clearly encourages a model that is proce-

durally driven and one that provides differentially enhanced financial rewards to perform more, not less, revascularization.

Finally, given the spiraling health care costs that we have witnessed in the United States over the past decade, and the financial burden this places on our existing health care system, businesses, and health care consumers, we certainly have abundant scientific evidence to support a more selective, measured, and balanced approach to the initial management of SIHD[1-8] and one that promotes and embraces optimal medical therapy for the majority of patients as a proven alternative to revascularization. With such an evidence base derived from multiple RCTs and meta-analyses, what more will it take to turn the tide of treatment for patients with SIHD and chronic angina from a PCI-first to an OMT-first approach? While prospective studies are ongoing, comparing therapeutic approaches in patients with more extensive anatomic CAD and functional severity with moderate-severe ischemic burden, we should be more willing to accept and embrace existing, available medical evidence that can guide patient management in a manner that encourages balance, transparency, equipoise, and full disclosure of all available treatment options.

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EDITOR'S NOTE

Informed Strategies for Treating Coronary Disease

More than 1 million stents are implanted annually in the United States to treat coronary disease, in the continuing hope that they are more effective than medical therapy in preventing heart attacks and prolonging life, despite abundant evidence to the contrary. Despite the highly publicized COURAGE findings, fewer than half of Americans with stable CAD who undergo stent placement have received medical therapy first. This latest meta-analysis, looking at recent PCI trials, again finds no benefit of PCI compared with medical therapy. Increasing use of American College of Cardiology Appropriate Use Criteria and realigning incentives for evidence-based approach will help improve quality of care. A "PCI first" strategy for patients with stable CAD gets a *Less Is More* designation because there is no known benefit and there are definite harms.

Rita F. Redberg, MD, MSc
Editor

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